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TESTS OF DEXTROAMPHETAMINE

Five-milligram tablets of Dextroamphetamine Sulfate, USP — ranging in price from 85¢ to $22.60 per thousand — were purchased from 38 pharmaceutical companies and tested for conformance to USP standards in the latest of a series of Medical Letter tests of prescription drugs. Both the 85¢ and the $22.60 samples were among those meeting official requirements.

For the first time in this series of tests, a drug other than that declared on the label was found in one of the samples. Instead of the dextro isomer of amphetamine, the tablets received from Cowley Pharmaceuticals contained dl-amphetamine; since the levo isomer is inactive, dl-amphetamine has half the milligram potency of dextroamphetamine. The same sample also failed to meet the USP requirement for speed of disintegration.

SUBSTANDARD SAMPLES - All except three of the other samples conformed fully to the official requirements. One sample contained an excess of the drug (128% of the labeled amount), and two samples showed excessive tablet-to-tablet weight variation. With 5-mg. tablets, the Pharmacopeia allows no more than two out of 20 tablets in a sample to deviate from the average weight of the tablets by more than 7.5%, with a maximum deviation in any one tablet of 15%. One sample (Faraday) showed a maximum deviation of 19%, with 10 of 40 tablets in the sample exceeding the 7.5% limit; in another sample (Darby), 9 of 40 tablets showed a deviation of more than 7.5%, but none of the tablets varied from the average by more than 11%. The latter sample also fell short of USP requirements in the disintegration test, with 5 of 18 tablets failing to disintegrate completely in 30 minutes.

Despite a general USP ban against the use of fillers which interfere with the extraction of a drug when it is assayed by a USP test method, some of the samples apparently contained such fillers. After consultation with Food and Drug Administration chemists familiar with the problem, a direct distillation method described in the 1955 edition of New and Nonofficial Remedies (AMA) was used with all samples that assayed at less than 95% by the USP method. Where a sample assayed higher by direct distillation, the higher figure is given in the table.

As in previous drug tests, all of the samples were purchased from the companies by pharmacists not associated with The Medical Letter. The samples, identified only by code numbers, were tested by a qualified commercial laboratory.

The following table shows the amount of dextroamphetamine in each sample (as a percentage of the labeled amount), and the price to the pharmacist of 1000 5-mg. tablets.

Company	Amount Present	Price per 1000
Allen Pharmacal (1)	128%	$2.00
American Drug Products	96	.85
American Pharmaceutical	97	3.60
Approved Pharmaceutical	97	3.00
Bryant Pharmaceutical	96 (D)	2.45
Carroll Chemical	103	2.50
Columbia Medical	97 (D)	1.60
Consolidated Midland	95 (D)	2.10
Cowley Pharmaceuticals (2)	—	2.30
Robert Daniels	100 (D)	2.25
Darby (Bio Intrasol) (3)	97	1.00
DuMont Pharmacal	99 (D)	1.20
Evron - yellow tablets	104 (D)	2.75
- orange tablets	91 (D)	3.25
Faraday Laboratories (4)	92 (D)	1.60
Gotham Pharmaceutical	100 (D)	1.25
Hance Bros. & White	90 (D)	2.95
Harvey Laboratories	92 (D)	1.75
Jan Laboratories	96 (D)	1.45
Lannett	101	1.60
Lustgarten Laboratories	96	1.75
H. L. Moore Chemical	100 (D)	1.00
Nysco Laboratories	100 (D)	1.50
Penhurst Pharmacal	98 (D)	1.45
Philadelphia Ampoule Labs.	92 (D)	1.02
Premo Pharmaceutical Labs.	94 (D)	3.00
Raway Pharmacal	100 (D)	1.30
Richlyn Laboratories	96 (D)	1.63
Robinson Laboratory	97	1.55
Smith Kline & French	101 (D)	22.60
Stanley Drug Products	96	1.50
Success Chemical	96	2.50
Supreme Pharmaceutical	100	3.28
Testagar	92	3.50
Vitamin Research	95	1.25
Vitarine	96	2.30
Wales Chemical	96	1.50
West-ward	93 (D)	3.05
Wolins Pharmacal	96 (D)	1.00

(1) Sample was substandard: dextroamphetamine content above 110% limit
(2) Sample labeled "dextroamphetamine," but tablets were dl-amphetamine
(3) Sample was substandard: weight variation excessive; failed to meet disintegration requirements
(4) Sample was substandard: weight variation excessive
(D) By direct distillation assay

DEPROL

In an appraisal of Deprol (Wallace), a combination drug offered for the treatment of mental depression, an early issue of The Medical Letter (1:92, 1959) said that the drug "is of no value for the treatment of either neurotic or psychotic depression." Despite the fact that Deprol has since become one of the most intensively promoted products on the ethical drug market, there is nothing in the more recent studies to justify a change in the earlier conclusion of Medical Letter consultants. [Depressions are generally subject to spontaneous remission, and many depressed patients respond to placebo therapy; nevertheless, most of the recent studies, like the earlier ones, were completely uncontrolled.] The purpose of this note is not to reiterate the previous judgment, but to point out the serious hazard to depressed patients in the high dosages now recommended in both medical journal and direct mail advertisements.

MEPROBAMATE DOSAGE - Deprol contains meprobamate, a sedative-tranquilizer, and benactyzine, an anticholinergic. Neither of these agents is effective against depression, but both are moderately safe when taken in small doses. The usual adult dose of meprobamate is 400 mg. three or four times a day; the package insert for Miltown, the Wallace brand of meprobamate, cautions that "doses above 2400 mg. daily are not recommended...." But the dosage range of Deprol recommended by Wallace (up to three tablets four times a day) contains as much as 4800 mg. of meprobamate. Continued dosage with much less than this amount can produce true addiction, with convulsions and other withdrawal symptoms.

The following statements about meprobamate in the Miltown package insert should be read with the knowledge that physicians are advised to use Deprol even for severe depression: "Careful supervision of dose and amounts prescribed for patients is advised; especially with those patients with a known propensity for taking excessive quantities of drugs.... The drug [meprobamate] should be given cautiously and in small amounts to patients who have suicidal tendencies" (our emphasis). There is no evidence that the addition of benactyzine to meprobamate makes meprobamate safe for patients with suicidal tendencies.

BENACTYZINE - The amount of benactyzine in the maximum recommended daily dose of Deprol is 12 mg. Benactyzine even in much smaller doses has many of the typical side effects of anticholinergic drugs, including dryness of the mouth, blurred vision, and tachycardia. "It has no advantages to compensate for these side effects or for the psychotic states it occasionally produces, especially when given in large doses" (The Medical Letter, 1:92, 1959). The possibility that benactyzine in the high doses suggested in Deprol advertising may aggravate incipient psychoses associated with depression has been raised by one Medical Letter consultant.

The clinical impressions and inadequately controlled trials supporting the claims for Deprol cannot conceal the absence of convincing evidence that this drug has any value except in cases amenable to placebo therapy; furthermore, the absence of warnings in the medical journal advertisements increases the hazard to depressed patients in the recommended high doses of Deprol. As The Medical Letter previously pointed out, "The chief danger in the promotion of this drug is that it will be given to seriously depressed patients, and that valuable time will

be lost before effective treatment is instituted. Nor can one disregard the possibility that some patients will get worse because of sedative effects and that others will suffer from withdrawal symptoms...."

DELVEX

The manufacturer of dithiazanine iodide (Delvex — Lilly) has warned physicians to use this anthelmintic drug with caution, since it is capable of causing serious and occasionally fatal reactions.

The brief history of Delvex in essence repeats the history of numerous other drugs which in early trials appeared to be safe, but which later proved to be hazardous. In the words of the Lilly letter, "Initial studies [reported in 1957] indicated a relatively low incidence of undesirable reactions with Delvex. However, subsequent experience in treating over one and a half million patients throughout the world has demonstrated an over-all incidence of gastro-intestinal side-effects (anorexia, nausea, vomiting, abdominal cramps, and diarrhea) of approximately 30 percent. In addition, on very rare occasions, fatal reactions have occurred...." According to a letter from the Lilly Research Laboratories, there is "a strong suspicion that in perhaps one-half dozen instances death may have been due to idiosyncrasy to Delvex."

DELVEX STILL USEFUL - Unlike many other drugs which could be discarded when they proved to be hazardous, however, Delvex retains an important place among anthelmintics. As the manufacturer points out, it is at present the only drug effective against Strongyloides stercoralis and Trichuris trichiura.

The manufacturer recommends the use of the drug for Strongyloides, for heavy infections with Trichuris, and for ascariasis only when other therapy has failed. Medical Letter consultants believe that even with Strongyloides and Trichuris infections, the drug should be used only when the parasites are causing overt symptoms, and that it should not be used at all in ascariasis. Piperazine (Antepar — Burroughs, Wellcome; and other brands) is the drug of choice for ascariasis; even when this drug fails, the infection does not have effects harmful enough to justify the use of Delvex.

Because of the frequency and the severity of toxic effects, Delvex should be used with caution in elderly persons, in patients with renal disease and disorders of fluid metabolism, and in patients with malabsorption syndrome. Whether the severe reactions to the drug are due to toxicity or to hypersensitivity is not known.

Where the use of Delvex is indicated despite its hazard, the manufacturer's directions should be carefully followed. (For a review of various anthelmintic drugs, see The Medical Letter, 2:4, 1960.)

THE MEDICAL LETTER MOVES - Between this issue and the next, The Medical Letter will move to new and larger quarters at 305 East 45th Street, New York 17, N. Y. After September 25th mail should be sent to the new address.

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